REMARKS

This is an amendment. Claims 1-6, 8-34, 36-58, and 102-103 remain in this application. By this amendment, claim 55 has been canceled without prejudice or disclaimer, claims 1-6, 8-34, 36-41, 44, 46-67, 49-50, 53-54, 56-57, and 102-103 are amended, and new claims 104-105 are added. No new matter is added. Support for the amendments and new claims is found throughout the specification and originally filed claims, such as at page 8, lines 18-20; page 13, line 25 to page 14, line 2; page 11, lines 6-11; page 11, line 17; and page 37, lines 23-36. Entry of this amendment is respectfully requested.

In addition to the amendments discussed below, Applicants note that claims 1-6, 8-34, 36-40, 49, 102-103 now recite vector rather than polynucleotide, in order to improve the clarity of the claims. Claims 1, 14, 17, 18, 19, 22, 26, 29, 36, 37, 38, 40, and 103 now recite "polynucleotide encoding a desired product" or 'desired product" rather than 'selected sequence encoding a desired product" or "selected sequence", in order to improve the consistency and clarity of the claims. Claims 17, 19, 22, and 29 now reference first and second polynucleotides encoding first and second desired products, respectively, in order to improve the clarity and consistency of claim language. Claim 44 now recites "DHFR-minus" (rather than "DHFR-"). Claims 49 and 50 now recite "GFP" rather than "green fluorescent protein" in order to improve consistency of the claims.

With respect to all new, amended, and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any objection and/or rejection made by the Office. Applicants expressly reserve the right to pursue prosecution of any subject matter not presently claimed in one or more future or pending continuation and/or divisional applications.

Pursuant to MPEP § 2001.06(b), the Examiner's attention is directed to the following co-owned, co-pending U.S. patent applications: USSN 10/714,000.

Information Disclosure Statements and Specification

Applicants note that the Examiner has not reviewed the Information Disclosure Statements that were submitted on May 13, 2004 (including 48 references) and October 18, 2004 (including 14 references). Applicants respectfully request that the Examiner review the references and return the initialed Form 1449s to Applicants.

The specification is amended to correct minor typographical errors. Entry of the amendments is respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-6, 8-34, 36-58 and 102-103

Claims 1-6, 8-34, 36-58 and 102-103 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite on the ground that the term "gene" is allegedly ambiguous and vague. Applicants respectfully traverse this rejection. Applicants respectfully submit that the meaning of the term "gene" is clear and that one of ordinary skill in the art would understand the scope of the term. However, to expedite prosecution, the claims have been amended as suggested by the Examiner, and now recite polynucleotide encoding an amplifiable selectable marker, polynucleotide encoding a GFP, polynucleotide encoding a desired product, and/or polynucleotide encoding a selectable marker. Withdrawal of this rejection is respectfully requested.

Claim 49

Claim 49 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse this rejection. Applicants submit that the term "expression" clearly refers to the expression of the green fluorescent protein gene *and* the amplifiable selectable gene. However, to expedite prosecution and clarify the claim, claim 49 has been amended and now recites "wherein expression of the green fluorescent protein and the amplifiable selectable marker is indicative of the cell also expressing the desired product". Withdrawal of this rejection is respectfully requested.

Claim 102

Claim 102 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite on the ground that "[a] GFP gene cannot be a GFP-fusion gene" and "[i]f [GFP gene] is to be interpreted to mean a gene encoding GFP then it cannot be the same as a GFP-fusion gene". Office Action, page 3. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the meaning of the claim is clear. As note in the last Amendment, the meaning of "GFP gene", as defined in the present application, encompasses a polynucleotide that encodes a GFP fusion protein. See, e.g., specification at page 10, lines 14-19; page 11, lines 10-11. Under MPEP § 2111.01III, where an explicit definition is provided by Applicants for a term, that definition will control interpretation of the term. Accordingly, the Examiner's interpretation of the phrase is improper. However, to expedite prosecution and not in response to the rejection, claim 102 has been amended and now recites "wherein the polynucleotide encoding the GFP is fused to a polynucleotide encoding a heterologous protein", as suggested by the Examiner. Withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-6, 8-9, 39-44 and 46

Claims 1-6, 8-9, 39-44 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Tan et al (US patent No. 6,235,967) ("Tan") as applied to or further in view of Chishima et al (Cancer Res. (1997) 57:2042-47) ("Chishima"). Applicants respectfully traverse this rejection.

The Examiner has not made a prima facie case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference(s) must teach or suggest all the claim limitation. See M.P.E.P. § 2143; see also *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dembiznak*, 175 F.3d 994, 999 (Fed. Cir. 1999).

A prima facie case has not been made because the Examiner has not demonstrated a suggestion or motivation to modify the reference, or a reasonable expectation of success.

As a preliminary matter, Applicants disagree with the Examiner's characterization of the present claims. For example, Applicants note that the phrase "operably linked" is explicitly defined in the present specification at page 18, lines 1-15. Under MPEP § 2111.01III, where an explicit definition is provided by Applicants for a term, that definition will control interpretation of the term. Accordingly, the Examiner's interpretation of the phrase is improper.

Tan neither teaches nor suggests the claimed invention. As noted by the Examiner, Tan teaches two embodiments, neither of which possesses each and every limitation of the claim invention. Specifically, the Examiner states that "[t]he '967 patent teaches a polynucleotide where GFP is fused to a selected sequence . . . and operably linked to a promoter . . . (e.g. Abstract, Fig. 1a)" and "the '967 indicates using a DHFR-GFP dicistronic vector (e.g. col. 6, Example 1; showing GFP-S65T mobilization into pED-mtx^r) . . .". (Office Action, page 5, 6).

The Examiner has not demonstrated suggestion or motivation to modify Tan or combine Tan teachings. The suggestion or motivation to modify the prior art must be found in the prior art, not in Applicants' disclosure. *See In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). The Examiner provides the following as evidence of motivation to combine:

> in essence, the '967 patent all but reduces to practice what is missing. For example, a GFP-target fusion is taught with a selectable marker. (e.g. Fig. 1a). the '967 patent teaches that a dicistronic vector comprising both a fluorescence encoding gene (i.e. GFP) and an amplifiable selectable marker (i.e. DHFR) can be used (e.g. col. 9, ll 40-45). In addition the '967 patent teaches that said

> polynucleotides can be used for production of a fusion protein (e.g., GFP-T antigen). (e.g. col. 9, ll. 50-51). Therefore, the '967 patent provides the motivation to construct a vector comprising a gene encoding a fluorescence marker, an amplifiable selectable marker and a target protein (Office Action, page 5).

However, the Examiner has mischaracterized the Tan specification in the above-quoted excerpt. Specifically, Tan at column 9, lines 40-52 relates to the construction of a retroviral expression vector for GFP, and describes the expression vectors depicted in Figures 1a and 1b. These vectors possess GFP fused to a selected sequence, methioninase or T-antigen. Thus, the vectors described at column 9, lines 40-45 of Tan do *not* comprise both a fluorescence encoding gene and an amplifiable selectable marker, contrary to the Examiner's statement in the rejection, nor does column 9, lines 50-51, of Tan state that vectors comprising a fluorescence encoding gene and an amplifiable selectable marker can be used for production of a fusion protein such as GFP-T antigen, contrary to the Examiner's statement in the rejection.[1] Therefore, Tan at column 9, lines 40-52 does not "all but reduce to practice what is missing", but rather teaches a Tan embodiment that the Examiner has acknowledged (elsewhere in the Office Action) does not contain each and every limitation of the claimed invention. It is evident, thus, that Tan does not provide motivation to construct a vector comprising a gene encoding a fluorescence marker, an amplifiable selectable marker and a target protein. Withdrawal of this rejection is respectfully requested.

The Office Action also states

> the ordinary skilled artisan, seeking to develop a construct for expressing proteins that can be easily be monitored via fluorescence and that can be selected for in mammalian cells via amplifiable markers such as DHFR, would have been motivated to incorporate the teachings of the '967 patent or Chishima et al. to construct a expression construct comprising GFP, a selected sequence and DHFR, operably linked to a promoter. (Office Action, page 6).

However, the Examiner does not provide any evidence based in the prior art in support of the above-quoted statement. Instead, the Examiner appears to rely on Applicants' invention for motivation, which constitutes unacceptable hindsight. *See In re Dembiznak*, 175 F2d 994 (Fed. Cir. 1999). Further, Chishima adds nothing to the Tan disclosure because Tan itself notes that Chishima discloses one embodiment of Tan (see Tan, column 1, lines 60-67), and each aspect of Chishima described by the

[1] For the record, Applicants note that the Examiner's statement at page 5, lines 3-4, of the Office Action is also inaccurate.

Examiner is also described in Tan. Accordingly, Chishima is cumulative of Tan. Withdrawal of this rejection is respectfully requested.

The Examiner has also not demonstrated that there is a reasonable expectation of success. The reasonable expectation of success must be founded in the prior art, not in the Applicants' disclosure. See In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). By contrast, in the rejection, the Examiner merely states that "given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said artisan would have had a reasonable expectation of success in practicing the claimed invention". (Office Action, page 6). The Examiner does not explain, however, how the prior art provides a reasonable expectation of success. A high level of skill in the art, as cited by the Examiner, does not overcome this deficit. The fact that a claimed invention is allegedly within the capabilities of one of ordinary skill is not sufficient to establish prima facie obviousness. *See* MPEP 2143.01. Withdrawal of this rejection is respectfully requested.

Applicants further submit that there was no reasonable expectation of success. As noted in the specification at

> initially, the integrity of the integrated expression vector and of the transcriptional linkage between the product gene of interest and the amplifiable gene as well as the GFP reporter gene upon amplification, was not predictable. It was possible that the gene of interest and/or the GFP gene may be deleted during amplification, as was previously reported with the DHFR gene (Kaufman et al. Mol. & Cell. Biol. 12: 1069-1076 (1981); Kaufman and Sharp, J. Mol. Biol. 159:601-621 (1982).

With respect to claims 8 and 9, Applicants respectfully submit that neither Tan nor Chishima teach or suggest a fusion polynucleotide, wherein the polynucleotide encoding the amplifiable selectable marker is fused to the polynucleotide encoding GFP, wherein the fusion polynucleotide is operably linked to the promoter. Withdrawal of this rejection is respectfully requested.

For the above-stated reasons, Applicants respectfully request withdrawal of this rejection.

Claims 47-48

Claims 1-6, 8-9, 39-44 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Tan et al (US patent No. 6,235,967) ("Tan") or Chishima et al (Cancer Res. (1997) 57:2042-47) ("Chishima"), and further in view of Moir and Mao (Bioprocess Technol. 1990 57:42-47) or Lubiniecki and Lupker (Biologicals. 1994, 22(2): 161-9). Applicants respectfully traverse this rejection.

As noted above, neither Tan nor Chishima teaches or suggests the claimed invention.

Moir teaches that proteins of interest can be targeted, or secreted, to the culture medium for production of those proteins from the recombinant cells of various host organisms. Lubinecki teaches that secreted or expressed proteins may be purified.

Moir and Lubinecki have not been combined as references or applied individually to assert unpatentability due to obviousness. Even so, Moir and Lubinecki do not disclose or suggest the claimed invention. Therefore, the cited references, in any combination, do not render Applicants' claimed invention obvious.

SUMMARY

Applicants believe that this application is now in condition for allowance and respectfully requests that the outstanding rejections be withdrawn and this case passed to issue. No new matter has been introduced, and entry of these amendments is respectfully requested. The Examiner is invited to contact the undersigned at (650) 467-6222 in order to expedite the resolution of any remaining issues.

This response/amendment is submitted with a transmittal letter and petition for a three-month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Respectfully submitted,
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Date: Mar 8, 2005

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